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A Comprehensive Analysis of Past, Present, and Prospective Strategies for the Optimal Management of T2DM

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Abstract

In the 21st century, Type 2 diabetes mellitus (T2DM) stands out as a critical metabolic condition, indicated by insulin deficiency and resistance stemming from various endogenous factors. The prevalence of T2DM is alarming, with projections indicating a surge from 366.2 million to 578 million cases by 2030 and an estimated 783 million individuals affected by 2045. In response to this global health challenge, extensive research has been directed towards identifying therapeutic targets to address T2DM. Numerous investigative efforts have focused on preserving the action of endogenous glucagon-like peptide (GLP)-1 by inhibiting the activity of Dipeptidyl peptidase IV (DPP-IV). Additionally, the exploration of peroxisome proliferator-activated receptor (PPAR- γ) agonists, the activation of glycation end products, stimulation of Diacyl glycerol transferase kinase pathways (DGAT-1), utilization of Sodium-glucose co-transporter 1 (SGLT-1) and SGLT-1 inhibitors, as well as the investigation of SIRT-1 agonists, have emerged as promising therapeutic avenues for managing T2DM. This review provides valuable insights into both current and novel targets in the pursuit of developing new drugs. These drugs, envisioned as potential monotherapies or components of combination therapies, hold the potential to function as dual-active agents in addressing the complexities of metabolic disorders. By understanding and leveraging these therapeutic targets, researchers and clinicians aim to develop innovative treatments that can significantly impact the management and mitigation of T2DM.

Keywords: Therapeutic Targets, Type 2 Diabetes Mellitus (T2DM), Hypoglycaemia, Hyperglycaemia, Insulin Sensitivity, Glucose Metabolism

Introduction

Diabetes Mellitus (DM) is a lasting metabolic illness distinguished by heightened amounts of glucose in the bloodstream. Two primary pathways contribute to its pathophysiology: autoimmune damage to pancreatic beta cells causing insufficient production of insulin, and inherent resistance of body cells to insulin activity, resulting in chronic hyperglycaemia [1]. The key types of DM are Type 1 (T1DM), Type 2 (T2DM), and Gestational Diabetes Mellitus (GDM), all causing interferences in carbohydrate, protein, and fat metabolism because of insulin imbalance [2]. T2DM arises from excess glucagon, inadequate insulin production, and insulin resistance [3,4]. Globally, DM poses a significant health challenge, with a substantial increase in cases over the years. In 2000, 151 million adults had T2DM, growing to 285 million by 2009 and currently affecting 463 million individuals aged 20–79 years. Projections indicate a further rise to 578 million by 2030 and 783 million by 2045 [5,6].

Current therapeutic classes for DM treatment consist of sulfonylureas, meglitinides, thiazolidinediones, biguanides, incretin mimetics, α -glucosidase inhibitors, among others. However, existing treatments often result in side effects like weight gain and hypoglycaemia, limiting long-term effectiveness [7,8]. Consequently, new approaches are emerging to enhance treatment efficacy and patient compliance. Promising targets under investigation include sodium–glucose co-transporter 2 inhibitors, insulin-releasing glucokinase activators, 11β -hydroxysteroid dehydrogenase 1 inhibitors, metabolic inhibitors of hepatic glucose, pancreatic G-protein coupled fatty acid receptor agonists, and glucagon receptor antagonists [9].

Current Therapies

Diabetes mellitus management involves a diverse array of therapies aimed at controlling blood glucose levels and preventing complications [10]. One widely prescribed medication is Metformin, recognized for its capability to lessen glucose production in liver and improve insulin sensitivity. Typically counted the first-line therapy for T2DM due to its effectiveness and relatively low risk of hypoglycaemia [11]. Sulfonylureas, such as glyburide and glipizide, stimulate insulin release from beta cells of pancreas [12]. Thiazolidinediones, like pioglitazone and rosiglitazone, enhance insulin sensitivity in peripheral tissues [13]. Meglitinides, represented by drugs like repaglinide and nateglinide, accelerate insulin release, especially in response to meals [14]. Alpha-glucosidase inhibitors, including acarbose and miglitol, slow down carbohydrate absorption in the gastrointestinal tract, particularly beneficial in controlling postprandial hyperglycaemia [15]. SGLT2 inhibitors, like canagliflozin and dapagliflozin, function by blocking glucose reabsorption in the kidneys, resulting in elevated urinary glucose excretion [16]. DPP-4 inhibitors, exemplified by sitagliptin and vildagliptin, inhibit the enzyme DPP-4, extending the duration of action of incretin hormones, which stimulate insulin release and reduce glucagon secretion [17]. GLP-1 receptor agonists, like exenatide and liraglutide, mimic incretin hormones, offering benefits such as improved insulin release and potential weight loss [18].

Insulin continues to be fundamental in the treatment of diabetes, especially for persons with T1DM and those experiencing progressive phases of T2DM. It directly replaces or supplements the body's insulin, ensuring adequate glucose regulation. Combination therapies, involving the simultaneous use of multiple medications with distinct mechanisms, are often employed to address various aspects of diabetes. The choice of therapy is individualized, considering factors such as the patient's specific needs, response to medications, and potential side effects [19]. Ongoing research aims to address side effects, leading to the development of novel drugs like SGLT2 inhibitors, DPP-IV inhibitors (e.g., sitagliptin, vildagliptin), GLP-1 inhibitors, Pramlintide, and PPAR inhibitors. In the management of T2DM, lifestyle changes involving diet, exercise, and weight reduction are emphasized. Metformin monotherapy is widely recommended, while insulin becomes the primary treatment for individuals exhibiting catabolic features such as polyuria, polydipsia, and weight loss. Continuous treatment is often necessary to maintain normal glycaemic levels throughout the diabetic lifespan [20,21].

Current antidiabetic medications for Type 2 Diabetes (T2DM) exhibit various side effects. For instance, sulfonylureas can lead to hypoglycaemia, while PPAR agonists like rosiglitazone are associated with obesity, fluid retention, malignant growth of the urinary bladder, and cardiovascular complications. Additionally, these medications often cause adverse effects like anorexia, abdominal discomfort, nausea, and more [7,22]. Increased insulin resistance, recognized as an oxidative stress illness, consequences of a variation in free radical formation and the body's natural antioxidant system, notably seen in elevated reactive oxygen species (ROS) production and reduced superoxide dismutase in diabetic patients [23].

To address these challenges, gene therapy and target-based treatments have emerged as advanced approaches in diabetes management, aiming to minimize side effects associated with conventional oral hypoglycaemic agents. Despite advancements, existing therapies face limitations, including issues like increased glucose uptake by the kidneys, hyperglucagonemia in alpha cells, and inadequate incretin levels [24]. The exploration of alternative therapies, such as Traditional Chinese Medicine (TCM), has shown promise as an adjunctive therapy for T2DM, reducing cardiovascular risk. Continued research has directed to the development of novel drugs, both synthetic and traditional, to improve the current landscape of diabetes treatment [25]. This review provides a comprehensive examination of newer targets, some already available as therapeutic drugs, while others are still in the research phase. These targets aim to offer more effective options for managing blood glucose levels in T2DM. The ongoing modernization of the global population is identified as a contributing factor to the increasing prevalence of this disease.

Information Sources, Search Methodology and Selection Criteria

For all target discussed in this review the best PDB IDs (Protein data bank identification number) were retrieved from RCSB Protein data bank. A thorough and organised search of the literature was conducted. The best PDB IDs for all the targets deposited approximately since last 5 years (If not any available than from previous years) in the RCSB PDB database is identified which are having resolution less than 2Å, homo sapiens organism is selected.

Current and Future Targets for the Treatment of Type II Diabetes Mellitus

For the management of T2DM, numerous newly discovered pharmacological targets have been identified (Table 1), including GLP-I, PPAR, PTP-1B, GPR 120,119,40, DPP-IV, DGAT 1 & DGAT 2 inhibitors, 5' AMP-activated protein kinase, fructose-1, 6-bisphosphatase, glucagon-like peptide 1, glucokinase, G protein-coupled receptor 119, glycogen synthase kinase 3, PTP1B, K⁺ Channels, PPAR- γ , SGLT2, α -glucosidase, etc. Metformin stands as the primary medication for T2DM, while the potential for future treatments lies in both multiple drug therapy and target-oriented approaches. Promising targets include α -amylase and adipokinase, marking a shift towards diversified treatment strategies [26]. Around 70% of individuals diagnosed with T2DM also experience hypertension. Initial treatment for hypertension in T2DM typically involves targeting angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARB) (Figure 1) [27].

Table 1.Targets for Anti-diabetic drugs action

Sr. No.	Targets for Metabolic disorders	Site of Action	PDB ID (Resolution Å)	Examples
1	Glucagon-like peptide receptor (GLP-I)	In pancreatic β cells (Coupled with G-protein subunits)	7S3I (2.51), 5OTU (1.8), 5OTT (1.92), 5OTV (2.0), 5OTX (2.0), 5OTW (2.1)	Exenatide, Liraglutide, Dulaglutide

2	Peroxisome proliferator-activated receptor-gamma (PPAR- γ)	Skeletal muscle cells and fatty liver	4CI5 (1.77), 4EMA (2.54), 5U5L (2.55), 6MD4 (2.24), 5Y2O (1.801), 5Y2T (1.7)	Pioglitazone, Rosiglitazone
3	Protein Tyrosine phosphatase (PTP1B)	Present in cells& controls Tyrosine phosphorylation	7KEY (1.771), 7KEN (1.8), 7KLX (1.839), 7MNC (1.85), 7FQO (1.93)	Ertiprotafib
4	G-Protein coupled receptor- GPR 120	Member of Rhodopsin family	8ID4 (3.1), 8ID8 (3.0), 8ID9 (3.0), 8ID6 (2.8), 8G59 (2.64)	-
5	G-Protein coupled receptor-GPR 40 & GPR 119	Member of Rhodopsin family	7WCM (2.33), 7XZ6 (2.8), 7WCN (2.87), 7XZ5 (3.1)	TUG-891
6	Dipeptidyl peptidase-IV (DPP-IV)	Inhibit the degradation of incretin and GLP-1	6B1E (1.77), 6B1O (1.91), 5T4B (1.76), 5T4E (1.77), 5T4F (1.9)	Sitagliptin, Saxagliptin, Linagliptin
7	Sodium-glucose co-transporter-2 (SGLT-2)	Present in PCT which prevents the reabsorption of glucose & facilitates excretion via the kidney	3DH4 (2.7), 2XQ2 (2.73), 7VSI (2.95)	Canagliflozin, Dapagliflozin, Empagliflozin
8	Diacylglycerol acyl transferase-I (DGAT I)	Stored in fats	6VY1 (3.0), 6VP0 (3.1), 6VZ1 (3.2)	LCQ-908 (Phase II), P7435 (Phase II)
9	11 β -hydroxysteroid dehydrogenase (11 β -HSD)	Present in organs, adrenal gland	4C7K (1.91), 4K1L (1.96), 5PGY (2.07), 4C7J (2.16), 6GMD (2.28)	BI 187004 (NCT02150824)
10	α -Glucosidase inhibitor	Brush the border of the small intestine	7QQH (2.25), 7QQF (2.43), 7QQG (2.43)	Acarbose, Miglitol, Voglibose
11	Glucose-6-phosphate amido transferase	Endothelial cell	2ZJ3 (1.9), 6R4F (2.5), 6ZMJ (2.77), 6ZMK	-

			(2.38), 7NDL (3.1)	
12	17 β -Hydroxy steroid hydrogenase type-I	Endometrium and placenta	7X3Z (2.25), 6MNE (1.86), 1QYX (1.89), 3DEY (1.7), 1QYW (1.63)	INCB13739, MK-0916, BVT.2733
13	Insulin receptors	B-cells of pancreas	8EYX (4.5), 8EYY (4.9), 8EZ0 (3.7), 6PSV (3.2), 6PXW (3.1)	-
14	Fibroblast growth factor 21(FGF21)	Cardiovascular system	4UXO (1.85), 3RHX (2.01), 6MZQ (2.0), 5EW8 (1.63)	Bimagrumab, PF-05231023, LY2405319
16	SIRT-I Agonists	Sirtuin 1/ NAD-dependent deacetylase sirtuin-1, is a protein that is encoded by the SIRT1 gene	4I5I (2.5), 4ZZH (3.1), 4ZZI (2.7), 4ZZJ (2.7)	Resveratrol, SRT1720

In Table 1 various anti-diabetic drug targets with their sites of action or the availability of that receptor in the living system are mentioned. The best PDB ID for the targets with the examples of drug acting on particular Pathways are also given in the table 1. Figure 1 provides the flow of physiological actions performed by various targets on the effector organ to maintain the metabolic processes.

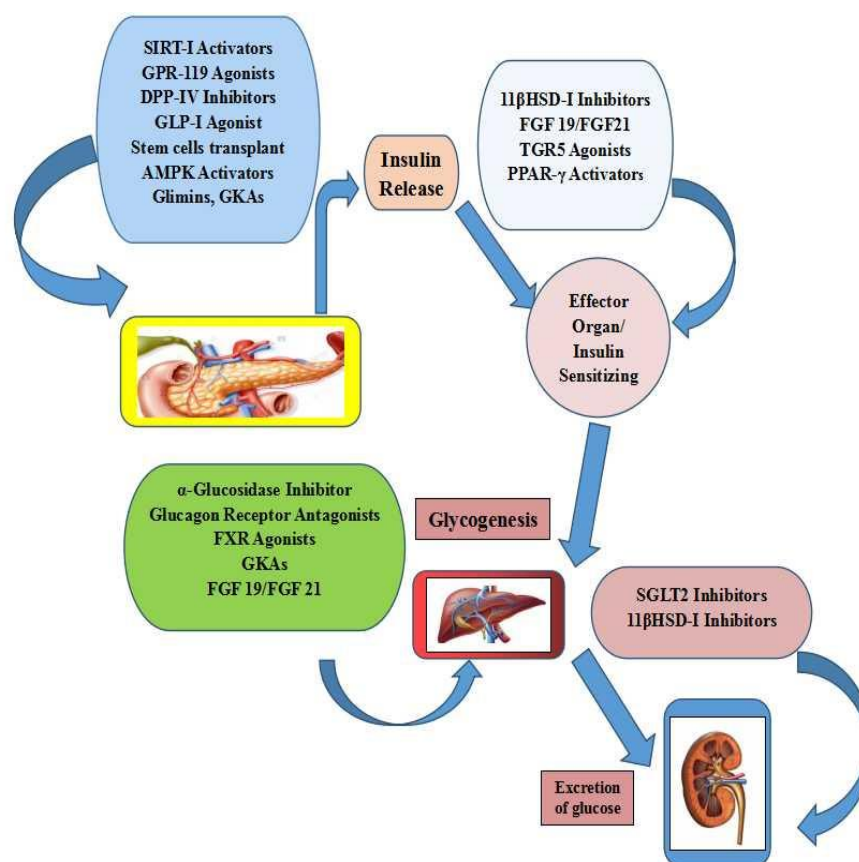


Figure 1. Anti-diabetic drug targets and site of action

Glucagon-like peptide 1 agonists

GLP-1 agonists bind and activate GLP-1 receptors present in pancreatic beta cells and various target tissues, including the brain, gastrointestinal tract, heart, and kidneys. Stimulation of these receptors on pancreatic beta cells prompts a glucose-dependent increase in insulin secretion, effectively regulating blood sugar levels. Simultaneously, these agonists reduce the secretion of glucagon from pancreatic alpha cells, thus reducing the glucose secretion into the bloodstream and further lowering blood glucose levels [28,29]. Additionally, GLP-1 agonists slow down the gastric emptying rate, postponing the absorption of glucose from ingested food and preventing postprandial blood sugar spikes. Notably, these agonists impact appetite regulation and satiety, fostering a sense of fullness and limiting food consumption, potentially leading to weight loss in individuals with T2DM. Drugs of this class are exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, and semaglutide [30].

Peroxisome proliferator-activated receptors gamma agonists

Peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG), commonly known as the glitazone receptor or NR1C3, is a nuclear receptor and transcription factor pivotal in the regulation of lipid metabolism and insulin sensitivity. Activation of PPAR-γ occurs through the binding of specific ligands, encompassing natural ligands like fatty acids and synthetic ligands such as thiazolidinediones (TZDs), commonly used in antidiabetic therapy. Following ligand binding, PPAR-γ undergoes a structural alteration enabling its heterodimerization with a different nuclear receptor known as retinoid X receptor (RXR). This heterodimeric interaction is key for PPAR-γ to exert its transcriptional regulatory roles. The PPAR-γ-RXR heterodimer binds to specific DNA sequences recognized as peroxisome proliferator response elements (PPREs) situated within the promoter regions of target genes. Typically

located in regulatory regions associated with lipid metabolism, glucose homeostasis, and adipocyte differentiation genes, PPREs play a pivotal role [31-33].

Once bound to PPREs, the PPAR- γ -RXR complex acts as a transcriptional activator, engaging coactivator proteins and modulating the transcription of target genes. This process leads to the either upregulation or downregulation of gene expression, depending on the specific target genes involved. Activation of PPAR- γ triggers a cascade of physiological effects linked to lipid breakdown and insulin sensitivity [34]. In adipose tissue, PPAR- γ facilitates adipocyte differentiation and lipid storage, ultimately decreasing circulating free fatty acids and enhancing insulin sensitivity. In peripheral tissues like muscle and liver, PPAR- γ activation boosts insulin sensitivity and facilitates glucose utilization, thereby contributing to improved glycaemic control. Thus, PPAR- γ stands as a critical regulator in metabolic pathways, offering potential avenues for therapeutic intervention in metabolic disorders such as T2DM [35].

Troglitazone, being the very first agent to be approved from this class was highly effective in controlling glycemia, since it has shown severe liver toxicity has been removed from the market. Pioglitazone and Rosiglitazone are PPAR- γ agonists presently used in the control of hyperglycaemia due to T2DM [13, 36].

Protein tyrosine phosphatase B inhibitors (PTP1B)

Protein Tyrosine Phosphate Non-Receptor Type 1 (PTP1B) is one of the important as well as attractive targets in the treatment of the T2DM which affects the sensitivity of the different types of cells towards the insulin. The gene that codes this PTP1B in humans is the PTPN1 gene. PTP1B works by dephosphorylating the phosphotyrosine residue in the cells that have activated insulin receptor kinase. The PTP1B acts in two steps [37]. It causes dephosphorylation of the p-Tyrosine substrate first. There is a nucleophilic attack at the phosphocenter by the reduced Cystein215 residue & protonation by Asparagine181 to yield neutral phenol. In the second step, the enzyme intermediates are broken down. The active enzyme is again regenerated once the intermediate known as thiophosphate is hydrolysed. This hydrolysis is facilitated by the hydrogen bonding interactions of Gln262 & ASP181[38]. Insulin receptor regulates the PTP-1B activity by self-degradation by tyrosine phosphorylation. Hence inhibition of this target PTP-1B will help to decrease insulin resistance, degradation of insulin stimulating receptors. PTP1B genetic deletion or pharmacological inhibition improved glucose homeostasis and insulin signalling without generating fat build-up in the liver, which is a benefit over other approaches [39].

Betulinic acid derivatives and guaiane sesquiterpenoids, along with Ursolic acid from *Cornus officinalis* fruits, exhibit PTP1B inhibition [40, 41]. The bioactive compound obtained from the *Cymbopogon citratus* have significant role in regulating the PTP-1B [42]. Ertiprotafib, a phosphotyrosine (pTyr) monocarboxylic acid mimetic, is the first PTP1B inhibitor subjected to clinical testing for diabetes management. In contrast to other anti-diabetic strategies, synthesizing effective small molecule inhibitors for PTP1B faces several difficulties due to its sequence similarities to other PTPs; nonetheless, surmounting these obstacles could open pathways to innovative approaches for addressing diabetes and associated cardiovascular issues [43].

G-protein coupled receptors 120, 40 & 119 agonists

The treatment of T2DM aims to boost insulin release by directly affecting beta cells or indirectly affecting enteroendocrine cells (CEE) of the gastrointestinal tract. The gastrointestinal tract expresses a variety of G protein-coupled receptor (GPCR) that regulates insulin release. A lot of research and development work has been done on these GPCRs, including specific GPCRs for free fatty acid ligands (lipid GPCRs), counting fatty acid receptor 1 (FFA1, also identified as GPR40), FFA2 (GPR43), FFA3 (GPR41) and FFA4 (GPR120), as well as gluconate receptor-dependent insulinotropic receptors that bind to lipid metabolites (GPR119). These lipid GPCRs control the intestinal and islet hormones [44]. GPR 120 works as a lipid sensor. Free fatty acids behave like gesturing molecules for GPR 10, GPR 41, GPR 84, and GPR 120. Upon activation, GPCRs leads to the secretion of incretin hormones,

such as glucagon-like peptide-1 (GLP-1), from intestinal L-cells. GLP-1 improves insulin release from pancreatic beta cells in response to glucose levels, promoting glucose homeostasis. Moreover, GLP-1 prevents the release of glucagon from pancreatic alpha cells, thereby aiding in the regulation of glucose levels [45, 46]. Since the discovery of TUG-891, the first synthetic agonist, study has cleared the path for the creation of TUG-based compounds and other chemical entities [47]. The synergic impact of the GPR119 agonist and DPP-IV inhibitor is useful for the improvement of novel hypoglycaemic drugs primarily based completely on the GLP-1-associated mechanism [48].

Dipeptidyl peptidase IV (DPP-IV) inhibitors

Dipeptidyl peptidase IV inhibitors (DPP-IV inhibitors) regulate glucose levels in blood by enhancing the effects of incretin hormones, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [49]. In the normal physiological state, incretin hormones are produced by the intestines in response to nutrient ingestion, stimulating the release of insulin from pancreatic beta cells in response to glucose and inhibiting the release of glucagon from pancreatic alpha cells. However, incretin hormones are quickly destroyed by the enzyme DPP-IV, leading to a shortened half-life and reduced effectiveness. DPP-IV inhibitors function by preventing the effect of this enzyme, thereby prolonging the action of endogenous GLP-1 and GIP. By preventing DPP-IV, these remedies improve the insulinotropic actions of GLP-1, resulting in heightened insulin secretion due to raised amount of glucose in the bloodstream [50, 51]. Simultaneously, they also reduce glucagon levels, limiting glucose production by the liver. These combined effects contribute to a lower postprandial glucose level, decreased fasting glucose, and improved overall glycaemic control in individuals with T2DM. Importantly, these drugs typically have a little possibility of hypoglycaemia, making them a favourable option for many patients [52]. Commonly prescribed DPP-IV inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin. Additionally, DPP-IV inhibitors have demonstrated efficacy in both standalone treatment and when used in blend with other treatments for diabetes, for example metformin, sulfonylureas, and thiazolidinediones [53-55].

Sodium glucose co-transporters 2 (SGLT 2) inhibitors

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2 inhibitors), commonly known as gliflozins, represent a novel category of medications that have picked significant consideration for their efficacy in managing T2DM. SGLT2 inhibitors exert their action by targeting a key pathway responsible for glucose reabsorption within the renal system, setting them apart from other antidiabetic medications and providing a unique and complementary approach to glycaemic control. Within kidneys, glucose filtration occurs in the glomeruli, leading to release of glucose in the renal tubules [56]. In normal circumstances, the majority of filtered glucose is reabsorbed back into circulation through sodium-glucose cotransporters, predominantly SGLT2, located in the proximal renal tubules. SGLT2 facilitates the reuptake of maximum of the filtered glucose. However, in people with diabetes, particularly those with poorly managed T2DM, the renal threshold for glucose reabsorption is elevated, resulting in better glucose reabsorption and subsequent hyperglycaemia [57].

SGLT2 inhibitors work by selectively inhibiting SGLT2 protein, thereby reducing glucose reabsorption in the renal tubules. By blocking the action of SGLT2, these inhibitors facilitate the excretion of excessive glucose in the urine, leading to decreased plasma glucose levels. This distinctive mechanism offers a unique approach to lowering blood glucose levels independent of insulin secretion or action, making SGLT2 inhibitors especially beneficial for individuals with T2DM who have insulin resistance or diminished insulin secretion [58]. Since SGLT2 inhibitors induce glucose excretion through urine, they are linked with modest weight reduction in individuals with T2DM. Furthermore, the osmotic diuretic effect resulting from increased elimination of glucose in urine can lead to reductions in blood pressure and intravascular volume. This dual action on weight and blood pressure makes SGLT2 inhibitors particularly advantageous for individuals with hypertension or heart failure. Moreover, these agents have been found to exert renoprotective effects by slowing the development of diabetic kidney disorder and reducing the risk of adverse renal outcomes [59, 60]. Empagliflozin, Dapagliflozin, canagliflozin, Ipragliflozin and Remogliflozin are few widely used SGLT2 inhibitors in the treatment of T2DM [61].

Diacylglycerol acyl transferase-I (DGAT-I) inhibitors

Diacylglycerol acyl transferase-I (DGAT-I) inhibitors exert their mechanism of action by modulating lipid metabolism, particularly through the selective targeting of the enzyme DGAT-I, which plays a vital role in triglyceride synthesis within cells [62]. Dysregulated lipid metabolism in individuals with diabetes frequently aids in the occurrence of insulin resistance and other metabolic complications. DGAT-I serves as the key enzyme in catalysing the conversion of diacylglycerol (DAG) and fatty acyl-CoA into triglycerides, the final stage in the triglyceride synthesis. By preventing DGAT-I activity, DGAT-I inhibitors decrease triglyceride production within cells, consequently lowering the overall levels of circulating triglycerides in the bloodstream [63].

By reducing triglyceride levels, DGAT-I inhibitors contribute to the alleviation of the disruption of insulin signalling. This, in turn, enhances the sensitivity of cells to insulin and improves the uptake of glucose by tissues, including muscle and adipose tissue [64]. Moreover, DGAT-I inhibitors have the potential to affect lipid partitioning and adipocyte function. Through the regulation of triglyceride production and deposition in adipose tissue, these inhibitors can contribute to the restoration of normal adipocyte function and the prevention of ectopic fat buildup in organs like the liver and skeletal muscle [65]. This phenomenon is frequently found in individuals dealing with insulin resistance and diabetes. Beyond influencing lipid metabolism and insulin sensitivity, DGAT-I inhibitors may also provide advantages in terms of weight management and cardiovascular health [66].

11 β -hydroxysteroid dehydrogenase-1 (11 β -HSD1) inhibitor

11 β -hydroxysteroid dehydrogenase-1 (11 β -HSD1) inhibitors signify a promising category of drugs for antidiabetic therapy which targets a key enzyme involved in glucocorticoid metabolism and have a key role in regulating glucose metabolism and insulin sensitivity. They exert their antidiabetic effects involves modulation of glucocorticoid activity and intracellular cortisol levels [67]. Glucocorticoids, such as cortisol, are steroidal hormones responsible for glucose metabolism and immune function. However, excessive glucocorticoid activity, particularly within adipose tissue and the liver, is strongly linked to the insulin resistance, altered glucose tolerance, and the development of T2DM. 11 β -HSD1 functions as an enzyme that facilitates the transformation of the inactive cortisone into its active component, cortisol, thereby intensifying local glucocorticoid action within target tissues. Inhibition of 11 β -HSD1 bring down intracellular cortisol levels and lower the side effects of additional glucocorticoids on insulin sensitivity and glucose homeostasis. By preventing the conversion of cortisone to cortisol, 11 β -HSD1 inhibitors effectively diminish glucocorticoid receptor activation and downstream signalling pathways implicated in insulin resistance and adipocyte dysfunction [68, 69].

Furthermore, 11 β -HSD1 inhibitors have been revealed to exert tissue-specific effects, primarily targeting adipose tissue and the liver, where glucocorticoid metabolism is most active. In adipocytes, inhibition of 11 β -HSD1 results in decreased adiposity, improved lipid profile, and enhanced insulin sensitivity, thereby reducing the development of obesity-related metabolic disorders. In the liver, suppression of 11 β -HSD1 activity leads to reduced hepatic glucose production and improved glycaemic control, which are key therapeutic goals in the treatment of T2DM [70]. Additionally, emerging evidence suggests that 11 β -HSD1 inhibitors may show valuable effects on pancreatic β -cell role. Severe exposure to raised cortisol amounts can impair β -cell function and promote the progression of T2DM. By lowering the harmful effects of glucocorticoid excess, 11 β -HSD1 inhibitors may help preserve β -cell function and promote insulin secretion, thereby aiding in the management of diabetes. The antidiabetic efficacy of 11 β -HSD1 inhibitors has been validated in preclinical studies and clinical trials, where these agents have demonstrated favourable effects on glucose metabolism and insulin sensitivity in persons with T2DM [71, 72].

 α -glucosidase inhibitor

Alpha-glucosidase inhibitors are category of medications commonly employed in the management of T2DM, which helps to regulate postprandial (after-meal) blood glucose amounts by decelerating the digestion and absorption of

carbohydrates [73] Normally, after the ingestion of carbohydrates, α -glucosidase facilitates the breakdown of complex sugars, such as oligosaccharides and disaccharides, into absorbable monosaccharides like glucose. These glucose molecules are then absorbed through the intestinal lining into the bloodstream, causing an increase in blood glucose levels. α -glucosidase inhibitors competitively bind to the active site of the enzyme and prevents its enzymatic action, delaying the excretion of glucose into the bloodstream, resulting in a slower and more controlled increase in blood sugar levels after meals [74]. Moreover, the delayed absorption of glucose also contributes to a reduction in insulin demand. Since blood glucose levels rise more gradually after meals in individuals taking α -glucosidase inhibitors, the pancreas is less burdened to produce large amounts of insulin to regulate glucose levels. This can help preserve pancreatic function over time and may also contribute to better long-term glycaemic control in individuals with T2DM [75].

Despite their effectiveness in reducing postprandial glucose levels and improving glycaemic control, α -glucosidase inhibitors are associated with certain gastrointestinal side effects like flatulence, bloating, and diarrhoea. These side effects occur due to the presence of undigested carbohydrates in the colon, which undergo fermentation by gut bacteria, leading to the release of gas and other byproducts. However, these side effects are generally mild and transient and often improve with continued use of the medication [76,77]. Acarbose, miglitol and voglibose are examples of α -glucosidase inhibitors that are commonly prescribed for managing diabetes. These medications are typically taken with meals to maximize their effectiveness in controlling postprandial glucose levels. While α -glucosidase inhibitors are not considered a first-line therapy for diabetes, they can be used alone or in mixture with other antidiabetic medicines to attain optimum blood glucose management [78].

Glucose-6-phosphate amidotransferase (G6PAT) inhibitors

Glucose-6-phosphate amidotransferase (G6PAT) is a major enzyme involved in the hexosamine biosynthetic pathway (HBP), which has a vital role in glucose metabolism and insulin signalling. Inhibiting G6PAT activity can potentially modulate various cellular processes related to glucose homeostasis, rendering it as an appealing target for antidiabetic therapy [79]. The mechanism of G6PAT inhibitors involves disrupting the activity of this enzyme, which has a pivotal role in the transfer of fructose-6-phosphate to glucosamine-6-phosphate in the HBP. By inhibiting G6PAT, these compounds can decrease the flux through the HBP, leading to decreased release of advanced glycation end products (AGEs) and other downstream metabolites that contribute to insulin resistance. AGEs are involved in the pathogenesis of diabetes-related difficulties, making G6PAT inhibition a potential therapeutic strategy for managing diabetes [80].

Moreover, inhibition of G6PAT can reduce the synthesis of UDP-N-acetylglucosamine (UDP-GlcNAc), a substrate for protein glycosylation reactions that show a role in insulin resistance and β -cell dysfunction. By lowering UDP-GlcNAc levels, G6PAT inhibitors may mitigate the abnormal glycosylation of insulin signalling proteins, thereby enhancing insulin sensitivity and glucose uptake in insulin-responsive tissues [81]. Furthermore, these inhibitors can alter the functions of transcription factors for example sterol regulatory element-binding protein 1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP), which control the expression of genes implicated in lipogenesis and gluconeogenesis. By inhibiting these transcription factors, G6PAT inhibitors can diminish hepatic glucose production and lipogenesis, thereby contributing to improved glycaemic control and lipid metabolism in those with diabetes. Along with their effects on glucose metabolism and insulin sensitivity, G6PAT inhibitors may also exert beneficial effects on other metabolic parameters associated with diabetes, such as lipid profiles and inflammation. By targeting multiple pathways involved in metabolic dysregulation, G6PAT inhibitors have the potential to offer comprehensive therapeutic benefits for controlling diabetes and its associated difficulties [82].

β Hydroxysteroid hydrogenase type-1 (11 β -HSD1) inhibitors

β -Hydroxysteroid dehydrogenase type-1 (11 β -HSD1) is an enzyme that exhibits a vital role in the regulation of glucocorticoid hormones, for example cortisol, within various metabolic tissues for example liver, adipose tissue, and skeletal muscle. Raised quantities of cortisol have been linked to insulin resistance and altered glucose metabolism,

aiding to the development of T2DM. Inhibition of 11β -HSD1 has emerged as a promising therapeutic plan for managing diabetes, and a number of inhibitors have been investigated for their potential as antidiabetic agents [83]. The mechanism of action of β -Hydroxysteroid dehydrogenase type-1 inhibitors involves the suppression of cortisol synthesis at the tissue level. 11β -HSD1 catalyses the transfer of inactive cortisone to active cortisol, thereby increasing the local concentration of cortisol within tissues. Elevated local cortisol levels, facilitated by increased HSD1 activity, lead to enhanced gluconeogenesis, adipogenesis, and lipolysis, ultimately contributing to insulin resistance and hyperglycaemia observed in T2DM. Inhibitors of this enzyme prevent the transfer of cortisone to cortisol, leading to reduced intracellular cortisol levels. By modulating cortisol activity, these inhibitors aim to alleviate insulin resistance and improve glucose uptake in peripheral tissues, ultimately improving glycaemic control in those with T2DM [84,85].

Moreover, 11β -HSD1 inhibitors exhibit tissue-specific effects, primarily targeting metabolic tissues characterized by elevated HSD1 expression levels. By selectively modulating glucocorticoid metabolism within these tissues, HSD1 inhibitors minimize the risk of systemic cortisol suppression associated with nonselective glucocorticoid receptor antagonists, thereby avoiding undesirable side effects such as adrenal insufficiency and immune suppression [86]. In addition to their direct effects on glucocorticoid metabolism, HSD1 inhibitors also show additional benefits such as reductions in visceral adiposity, improvements in lipid profiles, and attenuation of systemic inflammation, all of which are closely connected to insulin resistance and cardiovascular risk in individuals with T2DM. Clinical studies evaluating the therapeutic potential of HSD1 inhibitors like INCB13739, MK-0916 and BVT.2733 have shown promising results, demonstrating advances in glycaemic control and metabolic factors in persons with T2DM [83].

Insulin receptor agonists

Insulin receptor agonists, also known as insulin mimetics, represent a class of compounds intended to mirror the action of insulin in the body. They show a dynamic role in the management of T2DM, where insulin resistance and impaired insulin secretion are major concerns. Insulin receptor is a transmembrane protein found on the surface of target cells throughout the body. The insulin receptor consists of two extracellular α -subunits and two transmembrane β -subunits connected by disulfide bonds. The attachment of insulin to its receptor triggers a cascade of intracellular actions that regulate glucose metabolism, lipid synthesis, and protein synthesis [87]. Insulin receptor agonists function by attaching to the insulin receptor with high affinity, initiating a series of downstream signalling events similar to those triggered by endogenous insulin. Unlike insulin, which is subject to enzymatic degradation, insulin receptor agonists are designed to resist degradation, prolonging their half-life and therapeutic effects. Upon binding to the insulin receptor, agonists promote receptor autophosphorylation, whereby the β -subunits phosphorylate tyrosine residues on themselves and on intracellular substrates for example insulin receptor substrate (IRS) proteins. Phosphorylated IRS proteins function as docking sites for downstream signalling fragments, including phosphatidylinositol 3-kinase (PI3K) and Akt (protein kinase B). Activation of PI3K/Akt signalling pathways mediates the metabolic effects of insulin receptor agonists. Akt phosphorylates and activates several downstream targets included in glucose uptake, glycogen synthesis, and prevention of hepatic glucose production. One key target of Akt is the glucose transporter GLUT4, which translocates from intracellular vesicles to the cell membrane, enabling glucose uptake into skeletal muscle and adipose tissue [88].

In addition to promoting glucose uptake, insulin receptor agonists exert anti-lipolytic effects by inhibiting hormone-sensitive lipase (HSL) activity in adipocytes, thereby reducing circulating amounts of free fatty acids. This inhibition of lipolysis helps alleviate insulin resistance and hyperlipidaemia commonly observed in T2DM. Furthermore, insulin receptor agonists modulate gene expression and cellular metabolism through the activation of transcription factors for example sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptor gamma (PPAR- γ). These transcription factors regulate the expression of genes included in lipogenesis, adipocyte differentiation, and insulin sensitivity, supporting to the overall metabolic properties of insulin receptor agonists [89, 90].

Fibroblast growth factor 21 (FGF21)

Fibroblast growth factor 21 (FGF21) is a protein that has gathered significant attention for its potential as a beneficial candidate in the treatment of diabetes and related metabolic disorders. FGF21 is made and released primarily by the liver, but it is also present in other tissues for example adipose tissue, skeletal muscle, and pancreas. Its secretion is upregulated in response to numerous metabolic stresses, counting fasting, ketogenic diets, and glucose consumption. One of the primary mechanisms through which FGF21 exhibits its antidiabetic properties is by improving insulin sensitivity by promoting glucose acceptance in adipocytes (fat cells) and skeletal muscle, thereby reducing blood glucose levels [91]. Furthermore, FGF21 has been revealed to enhance lipid metabolism. It rises fatty acid oxidation in the liver and adipose tissue, which helps to reduce circulating amounts of triglycerides and free fatty acids. By promoting lipid breakdown and utilization, FGF21 can alleviate lipid buildup in tissues, which is often linked with insulin resistance and diabetes. Moreover, FGF21 has been associated with the regulation of glucose homeostasis through its impacts on pancreatic beta cells, which are accountable for producing insulin. Studies suggest that FGF21 may enhance beta cell function and promote insulin secretion, although the precise mechanisms involved are still being elucidated [92,93].

Several FGF21 agonists have been developed and investigated in clinical trials. One prominent example is the drug known as bimagrumab or BYM338. While initially developed as a treatment for muscle wasting disorders, bimagrumab has shown promise in preclinical and clinical studies for its metabolic effects, particularly in improving insulin sensitivity and reducing body weight. Bimagrumab works by binding to and activating FGF receptors, particularly FGFR1c, which subsequently triggers downstream signalling pathways that mimic the effects of endogenous FGF21 [94]. Another example of an FGF21 agonist is PF-05231023, developed by Pfizer. This compound has demonstrated efficacy in improving insulin sensitivity and lipid profiles in preclinical models of obesity and diabetes [95]. Other example is a synthetic FGF21 analog called LY2405319, which has demonstrated favourable outcomes in early-phase clinical studies. LY2405319 showed betterment in glycaemic control, lipid profiles, and body weight in patients with T2DM, highlighting the beneficial potential of FGF21 agonists in the management of metabolic disorders [96].

Sirtuin 1 (SIRT1) agonists

SIRT1 (Sirtuin 1) agonists have emerged as potential therapeutics for diabetes management owing to their ability to control several metabolic pathways involved in glucose homeostasis. SIRT1, a nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylase enzyme, shows a vital role in regulating cellular processes such as energy metabolism, stress response, and aging. The way by which SIRT1 agonists shows their antidiabetic effects primarily involves the regulation of key metabolic pathways. One significant pathway influenced by SIRT1 activation is the insulin signalling cascade. SIRT1 agonists promote insulin sensitivity by deacetylating insulin receptor substrate (IRS) proteins, which enhances their activity and facilitates downstream insulin signalling. This action helps improve glucose acceptance by peripheral tissues such as muscle and adipose tissue, thereby reducing hyperglycaemia [97,98].

Moreover, SIRT1 agonists modulate the activity of transcription factors included in glucose metabolism. For instance, SIRT1 activation inhibits the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and c-Jun N-terminal kinase (JNK), both of which are implicated in insulin resistance and inflammation. By decreasing NF- κ B-mediated inflammatory pathways, SIRT1 agonists mitigate the chronic low-grade inflammation commonly found in obesity and T2DM [99]. Another critical mechanism through which SIRT1 agonists exert their antidiabetic effects is by promoting mitochondrial function and biogenesis. SIRT1 activation enhances mitochondrial function by deacetylating and activating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), a principal controller of mitochondrial biogenesis and oxidative metabolism. Improved mitochondrial activity enhances cellular energy production, reduces oxidative stress, and improves insulin sensitivity. Furthermore, SIRT1 agonists have been shown to control hepatic glucose production by modulating the activity of key transcription factors involved in gluconeogenesis, for example forkhead box protein O1 (FOXO1) and peroxisome proliferator-activated receptor gamma (PPAR- γ). By inhibiting gluconeogenic gene expression in the liver, SIRT1 agonists help lower fasting blood glucose levels and improve glycaemic control in diabetic individuals [100].

Conclusion

With the universal epidemic of type 2 insulin-resistant diabetes mellitus fuelled by the rise of metabolic syndrome, depicted by obesity, insulin resistance, and dyslipidaemia, the need for innovative treatment approaches has never been more pressing. The evolving understanding of main pathogenic mechanisms, counting impaired glucose-stimulated insulin secretion and the function of lipotoxicity in insulin resistance, has unveiled novel molecular targets. From the exploration of G protein-coupled receptors sensitive to free fatty acids to the investigation of transcription factors like NRF2, promising avenues for therapeutic intervention continue to emerge. Advancements in drug discovery techniques, coupled with insights into disease pathogenesis, have led to the recognition of potential beneficial molecules. However, the development of new drugs is not without challenges, including issues of purity, toxicity, and specificity. Notably, emerging drug categories targeting SGLT-2 exemplify both progress and challenges, echoing the trajectories of previous breakthroughs like glucagon-like peptide-1 receptor ligands and dipeptidyl peptidase-4 inhibitors.

Looking ahead, continued research efforts will be crucial in unravelling the complexities of diabetes mellitus and translating scientific discoveries into clinically effective treatments. Collaborative endeavours across disciplines, from basic science to clinical practice, will be essential in driving innovation and addressing the evolving needs of patients worldwide. In this era of rapid scientific progress, the pursuit of emerging therapeutic targets offers hope for improved outcomes, enhanced quality of life, and ultimately, a brighter future for individuals living with diabetes mellitus.

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